Simulation of long-acting administration of antituberculosis agents using pharmacokinetic modelling

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Background

• Current anti-TB administration strategies are based on long-term oral dosing

• Oral administration is characterised by suboptimal adherence which represents a leading cause of treatment failure

• 20 to 50% of patients fail to complete existing tuberculosis treatment

• Injectable long-acting nano-formulations have been applied in numerous disease areas to simplify drug administration

• Long-acting administration of anti-TB agents could represent a valuable pharmacological strategy

Aims

- Design and validate a physiologically based pharmacokinetic (PBPK) model for existing oral anti-TB agents
- Simulate the pharmacokinetics of long-acting formulations of anti-TB agents in adult individuals
PBPK model

- Physiologically based pharmacokinetic (PBPK) modelling was used to inform the pharmacokinetics of anti-TB agents in adults
  - Mathematical description of absorption, distribution, metabolism and elimination processes defining pharmacokinetics
  - PBPK modelling integrates *in vitro* and clinical data to simulate drug distribution in virtual population
Parameter correlation

- % of body fat: \(((1.20 \times \text{BMI}) + (0.23 \times \text{Age}) - 16.2) \times \text{Weight} / 100\)
- Liver size: \(e^{-0.6786 + 1.98 \times \log(\text{Height})}\)
- Plasma protein: \(1.20 \times \text{BMI} + 0.23 \times \text{Age} - 16.2 \times \text{Weight} / 100\)
- Renal functions
- Cytochrome P450 expression
- Transporter expression
- Organ volume
- Regional blood flows
- Cardiac output

- Weight
- Height
- Ethnicity
- BMI
- Gender
- Age
Population variability

Essential PBPK Parameters

Virtual population

Variability
Intramuscular release rate

Metabolic clearance

Volume of distribution

\[ V_{ss} = (\Sigma V_{t} \cdot P_{tp}) + (V_{t}E: P) + V_{p} \]

\[ P_{tp: nonadipose} = \left[ P_{o:w} \times (V_{nit} + 0.3 \times V_{phl}) \right] + \left[ 1 \times (V_{wt} + 0.7 \times V_{phl}) \right] \times \frac{f_{uP}}{f_{u_t}} \]
Physiologically Based Pharmacokinetic Modelling to Inform Development of Intramuscular Long-Acting Nanoformulations for HIV

Rajith K. R. Rajoli · David J. Back ·
Steve Rannard · Caren L. Freel Meyers ·
Charles Flexner · Andrew Owen · Marco Siccardi
Study design

Validation

• Existing available oral anti-TB formulations of bedaquiline, delamanid and rifapentine were validated in adults
• Mean simulated values from 100 virtual individuals (aged 18-60 years) were compared with available clinical data

Prediction

• Virtual IM depot was included in the model to simulate IM administration
• Maximum feasible human IM dose of 2000 mg was assumed for pharmacokinetic predictions in the current study
• Release rate was selected in order to obtain maximal exposure over the dosing interval
Validation against clinical formulations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical</th>
<th>Simulated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>$C_{\text{min}}$ (µg/ml)</td>
</tr>
<tr>
<td>Bedaquiline (450 mg OD, single dose)(^1)</td>
<td>3.76 ± 1.17</td>
<td>-</td>
</tr>
<tr>
<td>Delamanid (300 mg OD, day 10)(^2)</td>
<td>0.41 ± 0.05</td>
<td>0.14 ± 0.04</td>
</tr>
<tr>
<td>Rifapentine (10 mg/kg OD, day 14)(^3)</td>
<td>21.7 (21.3-22.2)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^1\)AUC\textsubscript{0-24}; \(^2\)AUC\textsubscript{0-144}; \(^3\)van Heeswijk RP, Dannemann B, Hoetelmans RM., J Antimicrob Chemother. 2014 Sep;69(9):2310-8.

Deltyba, Assessment report, EMA, 2014.

Release rate optimisation

Release rate – 0.04 h\(^{-1}\)
Release rate – 0.004 h\(^{-1}\)
Release rate – 0.0004 h\(^{-1}\)

Therapeutic cut-off

Plasma concentrations (µg/mL) vs. Time (hr)
## Prediction - Summary

**IM Dose – 2000 mg/30 days**

**IM release rate – 0.0025 h⁻¹**

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC (Mean ± SD) (µg.h/ml)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (Mean ± SD) (µg/ml)</th>
<th>C&lt;sub&gt;trough&lt;/sub&gt; (Mean ± SD) (µg/ml)</th>
<th>Cut-off limit (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>271 ± 65</td>
<td>0.72 ± 0.16</td>
<td>0.14 ± 0.04</td>
<td>1.6 (ECOFF)</td>
</tr>
<tr>
<td>Delamanid</td>
<td>89 ± 16</td>
<td>0.23 ± 0.04</td>
<td>0.05 ± 0.01</td>
<td>0.04 (ECOFF)</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>1639 ± 160</td>
<td>4.12 ± 0.38</td>
<td>0.88 ± 0.09</td>
<td>0.06 (MIC)</td>
</tr>
</tbody>
</table>
Limitations

• Activity of transporters can affect distribution and elimination patterns

• Drugs with high lipophilicity tend to diffuse through the lymphatic circulation rather than through blood

• The technological complexities associated with reformulation may constitute a barrier for some anti-TB agents

• Long term stability of anti-TB agents in potential long-acting formulations is unknown
Conclusion

• This theoretical approach could assist in informing the design of long-acting formulation for IM administration of anti-TB agents

• PBPK modelling represents a predictive tool to rationalise anti-TB agent pharmacokinetics and hypothesise potential applications of long-acting anti-TB therapy

• Lack of clear pharmacodynamics cut-offs and clinical validation of alternative combinations complicates the selection of suitable long-acting candidates

• Long-acting formulations could also find potential application in the treatment of latent TB or chemoprophylaxis
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